1. The Claimed Embodiment Is Not Obvious

The Examiner alleges that the claims are obvious and unpatentable over Deng *et al.* (Canadian Patent Application 2,125,240 A1), and further in view of Yelton *et al.* (The Journal of Immunology 155:1994-2002 [1995]) and Hagiwara *et al.* (US Patent No. 5,589,573, issued 12/1996). Applicants cannot agree. There is no proper basis for the combination of the cited art. Moreover, even if the art is (improperly) combined, all of the elements of the presently pending claims are not taught.

A. There Is No Basis For The Combination

To establish *prima facie* obviousness, the Examiner must point to some motivation or suggestion within the references themselves, or within the knowledge generally available to one of ordinary skill in the art at the time of invention, to combine or modify the references. *See* MPEP §2143.01; *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Merely because the references ***could be*** combined or modified does not render the resultant combination obvious unless the prior art suggested the combination. MPEP §2143.01; *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990).

Applicants submit that the references cannot be considered collectively until the Examiner points to ***some motivation to combine*** those references. The purpose behind this requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent decision, articulates this position:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

See In re Rouffet et al., 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). It is readily apparent that the law of *In re Rouffet* requires the Examiner to present soundly reasoned arguments based upon the substance of the cited references.[1] Moreover, the law does not regard the Examiner as one skilled in the art. *See In re Rijckaert*, 28 USPQ2d 1955 at 1956

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[1] *Accord Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (stating that the examiner must present convincing line of reasoning supporting rejection).

(Fed. Cir. 1993)("[T]he examiner's assumptions do not constitute the disclosure of the prior art."); *See id.* at 1957 ("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears."). Indeed, the Federal Circuit has made it clear that "[b]road, conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614 (Fed. Cir. 1999).

i. The Office Action Does Not Address The Motivation Question

Applicants made the above-stated arguments previously - and yet, the Examiner has still not provided a sound basis for *combining* these references as required by the law in *In re Rouffet*. What the Examiner has provided is the unsupported and conclusory statement: "Thus it would be obvious to simultaneously produce mutations in the CDRs and in framework regions." (Office Action, p. 3).

The Examiner has provided no EVIDENCE that one skilled in the art would combine the teachings as suggested. The requirement that the Examiner make a showing of a suggestion, teaching or motivation is "an essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). There are three sources for this evidentiary component: the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). The suggestion most often comes from the teachings of the pertinent references. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998). Nonetheless, regardless of the source of the requisite evidence, the Examiner's showing "must be clear and particular . . . . ." *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999).

The Examiner has not satisfied the burden to present "evidence" that is "clear and particular." Of course, if the Examiner has knowledge of relevant facts which are used to make the rejection, the Examiner is free to used those facts - but only if submitted in the form of an affidavit. *See* 37 CFR 1.107(b). In the present case, the Examiner has submitted no such affidavit.

In sum, therefore, the Examiner only provides opinion and conclusory statements in support of the pending obviousness rejections. These opinions and conclusions may not be considered "evidence" and, in view of the above-cited case law, are inadequate to sustain a

rejection under 35 U.S.C. § 103. Accordingly, the claims are not obvious and should be passed to allowance.

Regardless of what Deng and Yelton teach, the Examiner has NOT shown that anyone of skill would combine the teachings. This requirement is a threshold requirement, i.e. the Examiner cannot speak of the combined teachings until the Examiner provides EVIDENCE as to why they would ever be combined.

ii. The Hagiwara Reference Does Not Involve Engineering

A review of Hagiwara reveals that it is NOT an antibody engineering reference, merely an antibody cloning reference with no apparent teaching to make changes in the sequence. Why would one skilled in antibody engineering even look to this reference?

This argument was made previously - and yet, the Examiner does not address it. This is not proper. When a rebuttal argument is made by an applicant, "the examiner must consider all of the evidence anew." *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785 (Fed. Cir. 1984).

iii. The Yelton Reference Only Involves CDR Changes

The Yelton reference only involves CDR changes and does not utilize the overlapping oligo approach as presently claimed. Why would one skilled in the art combine such disparate art and techniques? The Examiner is reminded that there are many techniques in use. The Examiner must provide a REASON for adopting the PARTICULAR technique from one reference and combining it with another.

This argument was made previously - and yet, the Examiner does not address it. This is not proper. When a rebuttal argument is made by an applicant, "the examiner must consider all of the evidence anew." In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785 (Fed. Cir. 1984).

B. Even If (Improperly) Combined, All Elements Are Not Taught

As noted above, the Examiner's obviousness argument is flawed because of i) failure to make the threshold showing of evidence necessary to justify the combination of teachings, and ii) failure to address applicants' fact-based argument that the references teach disparate techniques and thus would not be combined by one skilled in an antibody engineering. In this section, additional flaws are discussed, namely: iii) the mischaracterization of the Deng teachings and iv) the failure to take into account certain claim elements.

i. Deng Is Mischaracterized

The Examiner, relying on language in Deng on page 13, makes the following argument: "Deng specifically teaches randomization of not only CDRs but of the frameworks . . ." (Office Action, p. 3). However, it is respectfully submitted that the Examiner is mischaracterizing the language on page 13 of Deng by taking it out of context. When one skilled in the art reads page 13 of Deng in context, the following view is reached:

> "As one skilled in the art, I read this sentence to simply be summarizing that the Deng et al. approach can be used for either of the two applications discussed prior to the sentence, namely the maturation discussed on page 12 or the humanization discussed on pages 12-13. Thus, I do not read the sentence as teaching simultaneous changes in both the CDRs and the frameworks."

See Second Declaration of Dr. Watkins (paragraph 6). Thus, at the very outset, the Examiner is reading more into Deng than is properly taught.

ii. Simultaneous Changes Are Not Enough

In the immediately previous section, it is noted that the Examiner's position is based on a misreading of the language on page 13 of Deng. For purposes of argument (only), this section will assume the Examiner's characterization is true. Even if true, the Examiner's argument does not address the claimed embodiment. Importantly, "the Examiner cannot equate simultaneous changes with the simultaneous performance of grafting and reacquisition." See Second Declaration of Dr. Watkins (submitted herewith) (paragraph 6). It is not just a question of simultaneous changes; for Deng to teach the claimed embodiment, the changes must be shown to be in the context of grafting.

In this regard, the Examiner is requested to note that step "d" of Claim 42, for example, specifies combining the nucleic acid coding for frameworks with nucleic acid coding for modified *donor* sequences. The use of the donor sequences together with acceptor frameworks is the "grafting" element of Claim 42; the modification of the donor sequences and framework sequences is the reacquisition of affinity element of Claim 42.

The present specification notes (at page 17, lines 19-25) the advantages of not merely simultaneous changes, but simultaneous *procedures*:

> "[In prior art approaches]. . . once the CDR-grafted antibody, or variable region binding fragment is made, it requires subsequent rounds of molecular engineering to reacquire binding affinity comparable to the donor antibody. The present invention combines these steps such that CDR grafting and binding reacquisition occur in a single simultaneous procedure."

As noted by Dr. Watkins: "At no point in Deng et al. is it taught that these two *procedures* are to be performed in one step." See Second Declaration of Dr. Watkins (paragraph 4) submitted herewith. Indeed, "[a]t no point does Deng et al. provide either a teaching in the specification or an example where the two procedures of grafting and reacquisition take place in a single step. See Second Declaration of Dr. Watkins (paragraph 7) submitted herewith.

Thus, the Examiner's characterization of Deng - even if true - does not supply the elements presently claimed. On this basis alone, the Examiner's rejection must fail.

iii. Resurfacing Is Done In Deng By Different Rules

The Examiner makes a new argument in the Office Action. The Examiner refers to the "resurfacing" text on page 13 of the Deng reference and uses this text as a basis for arguing that Deng renders the claims obvious.[2] But this text of Deng et al. speaks of randomizing "exposed residues of the murine antibodies." As pointed out by Dr. Watkins:

> "This is not a selection of *which* residues to change based on two reference sequences 'that differ at the corresponding position' as presently claimed. This is a selection based on what residues are exposed' and thus is a completely different approach from the one presently claimed. Thus, even if both framework and CDR residues are taught to be changed in the Deng et al. resurfacing approach (something which the Examiner assumes without any explicit support in the text), the changes are being made using different rules than specifically required in the presently drafted claims."

See Second Declaration of Dr. Watkins (paragraph 3) submitted herewith. Thus, even if the Examiner's assumptions about resurfacing are correct, the resurfacing teachings of Deng do not supply the elements of the present claims. In this regard, the Examiner is asked to take note of step (b) of Claim 42 (by way of example), which reads in part:

> "wherein said framework positions of said modified heavy chain variable region that are changed *are selected from among* said acceptor framework positions of said second reference sequence that differ at the corresponding position compared to the donor framework positions of said first reference sequence"

This language of Claim 42 makes it clear that the rules of selecting positions for changes are governed by a comparison - not by which residues are "exposed."

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[2] The Examiner argues (at page 3 of the Office Action) that "it is obvious that resurfacing would result in randomization of both framework and CDR as both of these are surface exposed residues."

iv. Deng Teaches Away

Interestingly, the abstract of Deng *et al.* apparently teaches away from the simultaneous modification of CDR and FR residues, as it states that the method can be used for randomizing antibody complementarity determining regions **or** framework regions (emphasis added). This is reiterated on page one of Deng *et al.* (lines 11-15), where the invention is said to be exemplified with methods for randomizing antibody complementarity determining regions **or** framework regions (emphasis added).

This argument was made previously - and yet, the Examiner does not address it. This is not proper. When a rebuttal argument is made by an applicant, "the examiner must consider all of the evidence anew." In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785 (Fed. Cir. 1984).

v. Simultaneous Grafting And Reacquisitioning Is Counterintuitive

The Second Declaration of Dr. Watkins (submitted herewith) introduces new rebuttal evidence. Among other arguments, Dr. Watkins points out:

> "It is somewhat counterintuitive to perform grafting and reacquisition in one step. Most prior art methods first evaluate the degree to which grafting has caused the loss of affinity - *before* attempting to reacquire it. The presently claimed method, however, assumes that grafting alone will result in lower affinity."

See Second Declaration of Dr. Watkins (paragraph 8) submitted herewith. In other words, prior art approaches wait to see what damage is done to affinity by grafting. Only then do such prior art approaches attempt to remedy the damage. Thus, the presently claimed embodiment reflects an understanding of i) a problem that is not fully appreciated by the prior art (grafting will almost always cause a loss in affinity), and ii) the possibility of addressing the problem by doing more than merely grafting.

The Examiner is reminded that "a patentable invention may lie in the discovery of the source of the problem . . ." *In re Sponnoble*, 160 USPQ 237, 243 (CCPA 1969). MPEP 2141.02. The Examiner is also reminded that "solution of a different problem" is a secondary factor tending toward unobviousness. *See In re Wright*, 848 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988).

Most importantly, the Examiner - in the face of Dr. Watkins's fact-based Declaration - must start the analysis over:

"When . . . evidence is submitted in rebuttal, the decision-maker must start over . . .

> An earlier decision should not . . . be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability. . . . Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself."

In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976).

CONCLUSION

Applicants believe that the arguments set forth above[3] traverse the Examiner's rejections and therefore request that these grounds for rejection be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (617)-252-3353.

Dated: January 29, 2003

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[3] Applicants re-assert the "no polymerase" argument made previously (but do not repeat it here).